# Risk Assessment of Physiological Effects of Atmospheric Composition and Pressure in Constellation Vehicles[§]

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## Abstract

**Introduction:** To reduce denitrogenation time to prevent decompression sickness to support frequent extravehicular activities on the Moon, and to limit the risk of fire, a hypobaric ($P_B$ = 414 mmHg) and mildly hypoxic ($ppO_2$ = 132 mmHg, 32% $O_2$ - 68% $N_2$) living environment is being considered during lunar missions for the Crew Exploration Vehicle (CEV) and Lunar Surface Access Module (LSAM). If the vehicular ppO2 is acutely changed from 145-178 mmHg at standard vehicular operating pressure to less than 125 mmHg at desired lunar surface outpost operating pressures, there is the possibility that some crewmembers may develop symptoms of Acute Mountain Sickness (AMS). The signs and symptoms of AMS (headache plus nausea, dizziness, fatigue, or sleeplessness), could impact crew health and performance on lunar surface missions. **Methods:** An exhaustive literature review on the topic of the physiological effects of reduced ppO2 and absolute pressure as may contribute to the development of hypoxia and altitude symptoms or AMS. The results of the nine most rigorous studies were collated, analyzed and contents on the physiological concerns associated with hypobaric operations, AMS and hypoxia

symptoms summarized. **Results:** Although space vehicles have operated in hypobaric conditions previously, they have not operated in a mildly hypoxic ppO2. There is evidence for an absolute pressure effect *per se* on AMS, such that the higher the altitude for a given hypoxic alveolar $O_2$ partial pressure ($P_AO_2$), the greater the likelihood of an AMS response. About 25% of adults are likely to experience mild AMS near 2,000 m (xxx mmHg) altitude following a rapid ascent from sea level while breathing air (6,500 feet, acute $P_AO_2$ = 75 mmHg). The operational experience with the Shuttle staged denitrogenation protocol at 528 mmHg (3,048 m) while breathing 26.5% $O_2$ (acute $P_AO_2$ = 85 mmHg) in astronauts adapting to microgravity suggests a similar likely experience in the proposed CEV environment. **Conclusions**: We feel that the slightly elevated risk of AMS with the recommended exploration atmospheric parameters is offset by the DCS risk reduction and improved operational efficiency offered by the hypobaric lunar surface vehicular pressure. We believe the risk of mild AMS is greater given a $P_AO_2$ of 77 mmHg at 4,876 m altitude while breathing 32% $O_2$ than at 1,828 m altitude while breathing 21% $O_2$. Only susceptible astronauts would develop mild and transient AMS with prolonged exposure to 414 mmHg (4,876 m) while breathing 32% $O_2$ (acute $P_AO_2$ = 77 mmHg). So the following may be employed for operational risk reduction: 1) develop procedures to increase $P_B$ as needed in the CEV, and use a gradual or staged reduction in cabin pressure during lunar outbound; 2) train crews for symptoms of hypoxia, to allow early recognition and consider pre-adaptation of crews to a hypoxic environment prior to launch, 3) consider prophylactic acetazolamide for acute pressure changes and be prepared to treat any AMS associated symptoms early with both carbonic anhydrase inhibitors and supplemental oxygen.

## 1. Introduction

Future long duration spacecraft, spacesuits, lunar and Mars habitats are being developed at NASA centers, under the leadership of Johnson Space Center in support of the Vision for Space Exploration, also known as Constellation[35]. Several atmospheric design points for the Constellation missions have been developed by the Environmental Atmosphere Working Group (EAWG) ranging from normoxic to moderately hypoxic and normobaric to hypobaric[6]. These environments were analyzed to achieve a balance among the risk of decompression sickness, the overhead required to perform an exploration extravehicular activity (EVA), short and long term human performance at less than normoxic levels of partial pressure of oxygen ($ppO_2$), and the fire hazard. To limit the risk of fire, reduce the risk of decompression sickness and reduce the prebreathe time to support frequent extravehicular activities (EVAs) on the Moon, and later Mars, a hypobaric and mildly hypoxic living environment was proposed for the Crew Exploration Vehicle (CEV), the Lunar Surface Access Module (LSAM), and long-term surface habitats (Table 1).

**Table 1. Summary of Recommendations for Constellation Mission Systems**

| Vehicle | Nominal Total Pressure (psia +/- 0.2psia)[4] | Nominal Oxygen Partial Pressure (mmHg) [4] | Nominal Oxygen Concentration (% +/- 2.0 percentage points)[4] | Equivalent Air Altitude feet | Range of Total Pressure Capability (psia) [1] | Tissue Ratio (R) After 60 Minutes Prebreathing[3] |
|---|---|---|---|---|---|---|
| CEV to ISS | 14.7<br>10.2[5] | 160 ( 0 ft )<br>140 (3500 ft) | 21<br>26.5 | 0<br>4,000 | 0-14.9 | |
| CEV In-Space Suit | 4.3 | 222 | 100 | | 4.0-4.6 | 1.55 from 10.2 psia CEV to 4.3 psia suit |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lunar and Mars CEV | 14.7<br>10.2 | 160 ( 0 ft )<br>140 (3500 ft) | 21<br>26.5 | 0<br>4,000 | 0-14.9 | |
| Lunar and Mars Landers | 10.2<br>8.0 | 140 (3500 ft)<br>132 (5000 ft) | 26.5<br>32 | 4,000<br>6,000 | 0-14.9 | |
| Lunar and Mars Surface Suits | 4.3<br>6.0 | 222<br>310 | 100<br>100 | | 3.5-8.0 [2] | 1.13 from 8.0 psia Landers to 4.3 psia suit;<br><br>1.07 from 7.6 psia Surface Habitats to 4.3 psia suit |
| Lunar and Mars Surface Habitats | 8.0<br>7.6 | 132 (5000 ft)<br>126 (6500 ft) | 32<br>32 | 6,000<br>7,500 | 0-14.9 | |
| Mars Transit | 14.7<br>10.2 | 160 ( 0 ft )<br>140 (3500 ft) | 21<br>26.5 | 0<br>4,000 | 0-14.9 | |

Note 1: Range of total pressure capability covers Earth launch, Earth entry, and contingencies.
Note 2: Surface suit 3.5 psia capability for suit emergency operations, 8.0 psia for DCS treatment.
Note 3: 60 minute in-suit prebreathe is defined as the time in the suit after purge and leak check until absolute pressure on the body reaches 4.3 psia after a nominal depressurization.
Note 4: All nominal values are centers of control boxes assumed +/-0.2 psia total pressure, +/-2 percentage points oxygen.
Note 5: 10.2 psia recommendation is based on Shuttle experience, for CEV contingency EVA preparation.

The hypobaric and reduced oxygen environment is being recommended by the EAWG as an integrated solution to safety, engineering, operational, and medical concerns that have as their goal routine and safe exploration of the Lunar or Martian surface. Indeed, the Constellation program goals and proposed mission architecture emphasize EVA with exploration of planetary surfaces as the central driving operation. We present an analysis of risk of crew symptoms associated with proposed Constellation vehicle $O_2$ partial pressure ($ppO_2$). Extended exposures to even mild hypoxic stress can lead some to signs and symptoms of Acute Mountain Sickness (AMS). This is a concern in any aerospace application where mild hypoxia is deemed an acceptable trade. The goal of any trade process is an integrated product, and each stakeholder accepts a less than ideal outcome. Each stakeholder then develops a strategy to minimize the impacts of their less than ideal outcome. Our goal is to understand the risk of AMS, and then develop strategies to minimize any perceived risk.

### 1.1 Assumptions

Future vehicles for exploration missions will have less than atmospheric $P_B$, with a $ppO_2$ less than a sea level equivalent of 160 mmHg (3.07 psia). An efficient exploration program requires that EVA be efficient. The time to prepare for EVA should be minimal, and the suit pressure should be low to accommodate EVA tasks without undue fatigue, physical discomfort, or even suit-related trauma. Currently, a long prebreathe time is used prior to EVA from the Shuttle and the International Space Station to prevent DCS and significant venous gas emboli (VGE) insult of the lungs at low suit pressure. To shorten this prebreathe time, the habitat atmosphere should not have a high partial pressure of nitrogen ($ppN_2$). One practical approach to reduce the $ppN_2$ is to increase the $ppO_2$ while also reducing $P_B$. A balance must be achieved between the increased risk of fire at high $O_2$ concentration and the decreased risk of DCS as $ppN_2$ in the habitat is reduced. The concentration of $O_2$ and therefore the risk of fire for a given $P_B$ can be reduced if mild hypoxia is considered. So for good reasons, a modest hypobaric and hypoxic (HH) environment (see Table 2) with crews adapted to microgravity (μG) is one option for future Moon and Mars exploration.

**Table 2. Range of Atmospheric Conditions in Proposed Living Environments.**

| Environment | $P_B$ psia | $P_B$ mmHg | $F_IO_2$ (%) | $P_IO_2$ mmHg | $P_AO_2$* mmHg | Actual Altitude m | Actual Altitude feet | Equivalent Air Altitude m | Equivalent Air Altitude feet |
|---|---|---|---|---|---|---|---|---|---|
| **CEV + LSAM** | | | | | | | | | |
| **normal** | **8.0** | **414** | **32.0** | **117** | **77** | **4,877** | **16,000** | **1,829** | **6,000** |
| best case | 8.2 | 424 | 34.0 | 128 | 86 | 4,816 | 15,800 | 1,158 | 3,800 |
| worse case | 7.8 | 403 | 30.0 | 107 | 68 | 5,029 | 16,500 | 2,438 | 8,000 |
| **Habitat** | | | | | | | | | |
| **normal** | **7.6** | **393** | **32.0** | **111** | **71** | **5,182** | **17,000** | **2,286** | **7,500** |
| best case | 7.8 | 403 | 34.0 | 121 | 80 | 5,029 | 16,500 | 1,524 | 5,000 |
| worse case | 7.4 | 383 | 30.0 | 101 | 63 | 5,364 | 17,600 | 2,895 | 9,500 |

$P_IO_2$ is inspired $O_2$ partial pressure, computed as ($P_B$ mmHg – 47) $*$ $F_IO_2$ (as decimal percent).
* computed value is for an **acute** altitude exposure with a "typical" adult exhibiting a "typical" response to mild hypoxia. The exact value for $P_AO_2$ seen in the table would not likely be measured in a small sample of adults exposed to the conditions listed in the table.
When breathing an atmosphere that does not contain 20.9% $O_2$, it is helpful to determine the Equivalent Air Altitude by using the alveolar oxygen equation since most experience with hypoxia is with ascent to altitude while breathing air.

### 1.2 Unknowns

The nominal Equivalent Air Altitudes of 6,000 and 7,500 feet do not reflect the complete hypoxic stress since current literature indicates that AMS is a function of both the alveolar oxygen partial pressure ($P_AO_2$) and the total ambient pressure ($P_B$). It is unclear how to combine the two components of hypoxic stress to understand the true risk of AMS. Superimposed on physiological adjustments to living in a hypobaric hypoxia (HH) environment are physiological adjustments associated with adaptation to microgravity (μG). There is a concern that the combination of these stresses will degrade the health and performance of astronauts who must maintain a high level of proficiency to accomplish mission goals.

Superimposed on physiological adjustments to living in a HH environment are physiological adjustments associated with adaptation to μG, particularly a significant increase in blood viscosity. There is some uncertainty on the full impact that the combination of these stresses will have on the health and performance of astronauts who must maintain a high level of proficiency to accomplish exploration mission goals. Therefore, it is prudent to recommend an operational $ppO_2$ that does not fall into a physiological area of uncertainty, and to have a risk mitigation strategy for cases when operations push towards the limits of the known safe operational range.

**2. Methods**

An extensive review of the current database of altitude physiology, alterations in physiology occurring with exposure to microgravity, characteristics of materials exposed to various environmental atmosphere conditions, and prior spaceflight mission technical reports was conducted. This report provides responses to the three important questions related to AMS:.

1. Is there an absolute $P_B$ effect *per se* on the risk of AMS induced by HH?
2. Is there an increased risk of AMS when HH is combined with adaptations to μG?
3. Is there an amplified increase in blood viscosity when HH is combined with adaptation to μG?

The following sections review current literature about AMS and pertinent literature about adaptive changes in simulated or actual μG exposures, with and without additional hypoxic stress. Since significant uncertainties do exist to resolve the above questions, a risk mitigation

plan must be developed to minimize the impact of mild hypoxia combined with adaptation to μG.

## 3. Results

### 3.1 The Risk of AMS

Roach [3] says that quick ascent to altitudes over 2,590 m (8,500 ft) often results in symptoms of AMS. Nearly 25% of people are affected even at 1,981 m (6,500 ft) [3-5]. Others [6] find no significant symptoms below 3,048 m (10,000 ft). Many factors modify the risk of AMS between 1,981 and 3,048 m, particularly the rate of ascent to altitude, activity level at altitude, and individual susceptibility. One reality about NASA space vehicles is that depressurization to a final hypobaric $P_B$ can be on the order of minutes and not hours or days, although a more gradual pre-down approach could be instituted.

AMS is a constellation of signs and symptoms including headache, nausea, dizziness, fatigue, and sleeplessness that develops over a 6 – 24 hour stay in a hypoxic environment, usually from rapid ascent to altitude while breathing ambient air [7]. The headache, for example, is usually throbbing, bitemporal or occipital, typically worse during the night and on awakening, and made worse by Valsalva's maneuver, and combined with nausea can be likened to an alcohol-induced hangover. Additional clinical findings that confirm a diagnosis include changes in mental status, ataxia, peripheral edema, or changes in performance. A change in performance means that any of the above symptoms or clinical findings have caused a reduction in normal activities.

#### 3.1.1 Data for Pressure Effect *per se* on AMS

The Alveolar Oxygen Equation (AOE) was applied to several tests referenced in this report [8]. It is the key physiological variable to associate changes in the breathing environment to changes in other physiological systems. The acute respiratory changes, hyperventilation with the resulting increase in respiratory exchange ratio (RQ), caused by hypoxic stress induced from an ascent to altitude while breathing air or from breathing a hypoxic atmosphere while at sea level make it difficult to understand the resulting $P_AO_2$ without the aid of this equation. Also, the disproportionate contribution of water vapor toward decreasing $P_AO_2$ as $P_B$ decreases is managed in the AOE.

$$P_AO_2 = F_IO_2 * (P_B - 47) - P_ACO_2 * [F_IO_2 + ((1 - F_IO_2) / RQ)]$$

where $P_AO_2$ is alveolar $O_2$ partial pressure (mmHg), $F_IO_2$ is inspired $O_2$ fraction (decimal percent), $P_B$ is ambient pressure (mmHg), 47 is the vapor pressure of water at 37 c (mmHg), $P_ACO_2$ is alveolar $CO_2$ partial pressure (mmHg), and RQ is the respiratory exchange ratio (unitless), equal to 1.0 when breathing 100% $O_2$.

Our goal was to evaluate results from tests where <u>computed</u> hypoxic $P_AO_2$ were very similar between two tests but with different $P_B$s. It is possible to achieve the same computed $P_AO_2$ under four different experimental conditions where $P_AO_2$ and ambient $P_B$ are manipulated. A 2 X 2 matrix of $P_AO_2$ and $P_B$ combinations is possible:

**NN** – normobaric normoxia, where $P_B$ = 760 mmHg and $P_AO_2$ = 103 mmHg (sea level control),

**NH** – normobaric hypoxia, where $P_B$ = 760 mmHg and $P_AO_2$ < 103 mmHg ($F_IO_2$ <21%),

**HN** – hypobaric normoxia, where $P_B$ < 760 mmHg and $P_AO_2$ = 103 mmHg ($F_IO_2$ >21%), and

**HH** – hypobaric hypoxia, where $P_B$ < 760 mmHg and $P_AO_2$ < 103 mmHg ($F_IO_2 \geq 21\%$).

The assumptions are that identical computed hypoxic $P_AO_2$ between two different tests should result in equivalent hypoxic responses, and that the computed $P_AO_2$ is accurate. So if an equivalent hypoxic response is not observed, then it follows that it must be caused by something other than a difference in $P_AO_2$. But $P_AO_2$ is extremely dynamic, and then there is individual variability in how the central nervous system in conjunction with the respiratory system reacts to mild hypoxia, both during an acute and chronic exposure. So the caveat is to consider computed $P_AO_2$ as a "best estimate", not as an absolute. Always consider the possibility that there is a true difference in $P_AO_2$ in two experiments that purport to be equivalent hypoxic exposures when identical computed $P_AO_2$ is offered as evidence of their equivalency.

The complex cardiovascular-pulmonary-cerebral-renal-hematological-endocrine response to a hypoxic environment is <u>assumed</u> to be identical whether you are in a hypoxic environment while at altitude in an otherwise comfortable altitude chamber or if you breathe an equivalent hypoxic mixture in the same altitude chamber at sea level $P_B$. This assumption has recently been called into question. The concept of equivalent air altitude exposure is that there is no difference in hypoxic response at any altitude as long as the same $P_AO_2$ is achieved at two different altitudes by breathing the proper supplemental $O_2$. The routinely applied notion of an "equivalent air altitude exposure" is invalid for higher altitude if it is true that there is an absolute $P_B$ effect on the risk of AMS, certainly if two different altitudes are supposedly equivalently hypoxic.

There are hundreds of reports about HH and hundreds of reports about NH, but unfortunately there are fewer than nine reports where the combination of HH and NH were tested together or HH, NH, and HN were tested together to specifically look for a $P_B$ effect *per se* on AMS. The sum total are listed here in ascending chronological order: Tucker [9-10], Grover [11], Levine [12], Roach [13-14], Loeppky [15-16], Savourey [17], and Leoppky [18].

Two of these studies [10] [14] speak directly to the AMS scores, while the others document physiological measurements that show a difference between HH and NH exposures even though computed $P_AO_2$ between the test are similar. Tucker [10] takes men already living at 1,524 m (5,000 ft) altitude in Colorado ($P_AO_2$ = 77 mmHg from AOE) to either 4,572 m (15,000 ft) while breathing air in an altitude chamber or while at site pressure breathing a hypoxic mixture (about 14% $O_2$ and 86% $N_2$) such that computed $P_AO_2$ for the HH and NH exposures are about 45 mmHg. Even though the arterial blood $O_2$ saturation was about 81% in both tests, the mean AMS score (not based on Lake Louise system) for the NH exposure was 3.2 compared to 6.7 for the HH exposure. Roach [14] and Loeppky [15] [18] confirm this basic observation with men also living at 1,524 m altitude in New Mexico. Again, an ascent to 4,572 m while breathing air in an altitude chamber was compared to breathing a hypoxic mixture at site pressure. The AMS scores (based on Lake Louise system) increased from 2.0 to 3.7 in Roaches' work, while Loeppky confirms that modest hypoventilation [16] combined with mild edema [18] under HH relative to NH conditions likely explains the differences in AMS scores.

So there appears to be a $P_B$ effect *per se* at work on physiological responses and signs and symptoms (onset time, incidence, and severity) of AMS based on a review of literature from 1980 to the present [19]. This statement is "conditional" on the fact that hypoxia is present. The

current research says that you should not assume all AMS outcomes would be equivalent given only equivalent hypoxic $P_AO_2$. This has led to the clinical observation that the most effective treatment for AMS is the application of increased $P_B$ to achieve a particular treatment $P_AO_2$ instead of increasing the percentage of $O_2$ at the current lower $P_B$ to achieve the same treatment $P_AO_2$ [20].

### 3.1.2 Body Fluid Balance and RBC Changes in Microgravity

The adaptive response to μG exposure is a reduction in total body fluid [21], followed by a reduction in red blood cell (RBC) mass over a longer period, but with little change in hematocrit (HCT) in the absence of hypoxic stress [22]. Prior to the reduction in body fluid there is cephalic shift of fluid leading to a loss of leg fluid volume, with excess fluid distributed into the face and chest. Pulmonary capillary blood volume increases by about 25%. The initial fluid shift increases stroke volume. Stretch receptors in the arterial circulation and in the heart sense changes in the central blood volume, so water immersion, supine or head-down bedrest and exposure to μG are all sensed as an increase in central blood volume. In response, there is a decreased renal sympathetic drive, a decrease in renin activity from the kidneys leading to decreased ALD secretion [23]. Plasma volume drops rapidly to about 17% [23]. Part of this reduction is due to loss of fluid to the extravascular space. There is a transient increase in HCT which would reduce erythropoietin (EP) secretion, which does decrease in space [24]. The net result in a normoxic environment is a reduction in RBC mass. In a significant hypoxic environment, EP production would be stimulated. Erythropoietin secretion requires altitude of about 2,500 m (8,200 ft) or greater, and exposures longer than six hours [25].

A dysfunction in the body's handling of water is proposed as one factor in the development of AMS. Individuals who show diuresis upon arrival at high altitude appear to function better than those who exhibit an antidiuresis response. The most affected subjects show a marked reduction in urine flow associated with elevated levels of ADH [18] [26]. It is not clear whether the increase in ADH is a response to net fluid loss into the extravascular space or the cause initiated by an unknown mechanism triggered by HH. Fluid shifts from the intravascular space to the extravascular space leads to edema, with significant problems if the result is cerebral edema or pulmonary edema. As mentioned earlier, there is a hypoxic component as well as a hypobaric component to AMS, and now fluid volume changes and redistribution associated with μG adaptation may contribute to AMS.

A concern with any decrease in plasma volume, with or without an accompanying edema, is that the rheological properties of the blood will change ultimately leading to impaired cardiopulmonary performance through a change in viscosity. Viscosity is a property of fluid related to the internal friction of adjacent fluid layers sliding past one another as well as the friction generated between the fluid and the wall of the vessel. This internal friction contributes to the resistance to flow. The viscosity of plasma is about 1.8-times the viscosity of water (termed relative viscosity) at 37°C and is related to the protein composition of the plasma. Whole blood has a relative viscosity of 3-4 depending upon HCT, temperature, and flow rate. As HCT changes in response to μG adaptation and HH, significant changes in blood viscosity become a concern.

It is known that deconditioning and fluid redistribution occurs during extended bedrest, bedrest with head down tilt, and exposure to μG. There is a decrease in total blood volume through a combined loss in plasma volume and RBC mass [27] [23] [28] [22]. Hematocrit

transiently changes during this period of adaptation, but returns to near-baseline values over several weeks in a NN environment. Exposure to significant HH leads to an increase in RBC mass with an expected increase in HCT [22] [29] and blood viscosity [30] [31]. An increase in HCT above 55% increases blood viscosity where the decrease in cardiac output more than offsets the gain in $O_2$ capacity of the blood. This combination leads to a decrease in $O_2$ transport [29] [32].

### 3.1.3 Potential Integrated Response

There are hundreds of reports about HH without μG simulation, and hundreds of reports about μG simulation under NN conditions. But the unfortunate reality is that there are fewer than 10 reports in the United States where the combination of HH and adaptation to μG were tested together. And in some of these reports the degree of μG adaptation was limited to just hours on a tilt table, so have limited application here. The sum total are listed here in ascending chronological order: Stevens [33], Lynch [34], Waligora [35], Fulco [36], Loeppky [37-39], and Whitson [40].

The increase in HCT from about 42 to 45% during 10 days of 6-degree head down bedrest from Martin [30] was similar to the increase from 43 to 46% for 6-degree head down bedrest after 28 hours reported by Waligora [35] with subjects exposed to 2,438 m (8,000 ft) altitude for eight hours, and the increase from 42 to 48% for supine subjects after 114 hours at 4,300 m (14,000 ft) reported by Fulco [36]. The results from Fulco [36] are similar to Stevens [33] and Loeppky [38-39]. They show increases from 43.6% to 50.9% and from 47% to 52% when head down bedrest over many days was combined with HH from ascent to between 3,048 and 3,657 m (10,000 and 12,000 ft). It is important to note that the baseline data from Loeppky with 47%

HCT is from subjects pre-adapted to living at about 1,524 m, but the difference of 5% from the combined head down bedrest and HH is comparable to the 6% difference from Stevens [33] and the 6% difference from Fulco [36]. There is no obvious negative synergistic interaction between HH exposure with μG adaptation that appears across the experimental conditions in six applicable reports.

### 3.2 Physiological concerns

The proposed spacecraft and habitat environmental atmosphere take into the account the following along with the inherent risk of developing AMS:

#### 3.2.1 Crewmember Physiology

Under standard atmospheric conditions of 14.7 psia pressure and $ppO_2$ 3.0 psia (159 mmHg), approximately 98% of the hemoglobin will be saturated with oxygen during passage through pulmonary capillaries. This is reflected in the oxygen-hemoglobin dissociation curve when the $P_AO_2$ is 100 mmHg. The $P_AO_2$ takes into consideration the dilutional effects of water vapor and carbon dioxide at the level of the alveoli, hence the lower value.

Technically, as the $P_AO_2$ falls below 100 mmHg (1.93 psia) the hemoglobin begins to desaturate, resulting in a relative "hypoxic" zone. Clinically, symptoms of hypoxia are not observed in healthy individuals until the $P_AO_2$ enters the steep portion of the curve, generally below 60 mmHg (1.16 psia) corresponding to a hemoglobin saturation of less than 90%. This corresponds to an equivalent altitude in non-acclimatized individuals of greater than 10,000 ft above sea level[11,17]

Interestingly, the amount of alveolar carbon dioxide, $P_ACO_2$, and water vapor pressure change little at this altitude, adding to the dilutional effects. Reduced atmospheric pressure with concomitant reduction in $P_AO_2$ below 60 mmHg has several acute effects including decreased mental proficiency, visual acuity, muscle fatigue, nausea, headache, and impaired discrete motor movements, [11,15,17] similar to what has been described as AMS.

### 3.2.2 The Risk of AMS on Constellation Vehicles

There was not an abundance of data or even a small amount of data specific to our environmental conditions. There were only four reports about a $P_B$ effect *per se* on the risk of AMS induced by HH and six reports on the combined effects of HH and simulated μG adaptation that have some application here. So all conclusions made here are based on extrapolation or interpolation from limited information. In this regard, it was verified with confidence that there is an absence of data specific to the exploration risk scenario. Even a small amount of best data are not directly applicable. Data from Roach, Loeppky, and Tucker are specific to subjects that lived for years at about 1,524 m altitude in New Mexico and Colorado. Clearly changes associated with these tests are less than expected if applied to subjects who ascend from sea level to the test altitude. In addition to the lack of applicable data, there is also a clear lack of data for women exposed to HH, to simulated μG adaptation, and the combination of HH and simulated μG adaptation.

There is one example where mild hypoxia is produced through the combination of enriched $O_2$ (>21%) under hypobaric conditions ($P_B$ < 760 mmHg) and has been used with hundreds of subjects over several days, with and without adaptation to μG. These data are from the ground

testing and good operation experience of the Shuttle staged denitrogenation protocol. The data are marginally applicable here since good operational experience is not equivalent to quality research data, and the Shuttle conditions are not identical to those currently planned for the CEV, and beyond. Subjects in an altitude chamber and later astronauts on the Shuttle spent hours to days at 10.2 psia (10,000 ft) breathing 26.5% $O_2$ as a means to partially denitrogenate body tissues prior to depressurization to 4.3 psia with 100% $O_2$. The $P_AO_2$ is computed at 85 mmHg during the staged protocol, equivalent to breathing air at 1,219 m (4,000 ft) if we discount the current discussion about the validity of applying the idea of "equivalent air altitude exposure". The point is that the good testing and operational experience with this protocol suggests that there is no significant negative synergy between very mild HH and μG. But it is an extrapolation to conclude anything about the worse case $P_AO_2$ of 68 mmHg at 5,029 m (16,500 ft) in astronauts adapting to μG in the CEV based on the literature reviewed for this report.

Although initial signs and symptoms of AMS in susceptible subjects are expected after prolonged exposure to between 1,981 m (6,500 ft at $P_AO_2$ = 75 mmHg) and 2,590 m (8,500 ft at $P_AO_2$ = 67 mmHg), it is likely that these would be self-limiting once acclimatization proceeds [3]. Roach [14] and Tucker [10] have the best data from which to conclude that AMS is very likely for some people exposed to 4,572 m (15,000 ft) with a $P_AO_2$ of about 45 mmHg in subjects pre-adapted to living at 1,524 m. Therefore, at 8.0 psia (4,876 m or 16,000 ft) with a nominal $P_AO_2$ = 77 mmHg in astronauts not pre-adapted to living at 1,524 m altitude it is likely that susceptible astronauts simultaneously undergoing adaptation to μG [38-39] will experience signs and symptoms of AMS. It is unlikely that a clinically significant increase in HCT will occur. A transient increase to a mean HCT of about 50%, possibly as high as 55% in a particular

crewperson, would be predicted based on the data [33] [38-39] for the combined effects of HH and adaptation to μG as envisioned for the CEV program. However, typical μG adapted spaceflight HCT values are in the low normal range, from 36-40% depending on gender.

There are several examples where the physiological changes initiated by HH and adaptation to μG are in opposite directions. Therefore, the net effect is a blunted response when both conditions occur simultaneously. For example, HH increases sympathetic drive through the release of catecholamines [36] [41] [42-43] while supine or head down bedrest reduces sympathetic drive (Volicer 1976)[need Ref]. HH increases RBC mass that is opposite the decrease seen in extended bedrest and exposure to μG [27]. Some even propose that the compensations for HH provide a beneficial therapy for cardiovascular deconditioning associated with extended bedrest [45-46] [34]. One example for a negative synergy is a possible enhanced reduction of the ventilatory response to hypoxia. The classic response to hypoxia is to increase ventilation, but the increase is slightly less if the hypoxia is caused by a hypobaric exposure compared to the same hypoxia caused in a normobaric condition [17]. Prisk [47] shows a reduction in ventilatory response to hypoxia in normocapnic subjects during supine and μG exposure compared to standing subjects. The notion is that increase in blood pressure due to body position modifies the ventilatory response to hypoxic challenge. The two studies are not directly comparable, but this may be a case where HH and adaptation to μG lead to a greater reduction in ventilatory response to hypoxia that either in isolation would cause. This is not an ideal situation if the goal is to avoid AMS associated with a suppressed ventilatory response to hypoxia. Rahn [48] even shows that hyperventilation on standing after being supine increases $P_AO_2$ as $P_ACO_2$ drops from about 42 mmHg to 37 mmHg in response to the hyperventilation. So body position modifies $P_AO_2$, and it is unclear how μG influences $P_AO_2$ given that body position is irrelevant. Finally, it can

be argued from the work of Loeppky [38-39] that HH and μG simulation produced changes that are additive. He shows an additional loss of plasma volume, with an additional increase in hemoglobin and HCT given a $P_AO_2$ = 59 mmHg at 3,361 m (10,700 ft) altitude in subjects exposed eight days to 5-degree head down bedrest compared to the loss of plasma volume and increase in hemoglobin and HCT in subjects just exposed to 3,361 m altitude. On balance, there is no definitive evidence for an exaggerated (negative synergistic) response to the combination of HH and adaptation to μG. On the contrary, the limited evidence suggests that one stressor tends to counteract the other.

In an attempt to understand the possible physiological interaction of hypoxia and microgravity, researchers at NASA Glenn Research Center analyzed existing data assuming a long duration mission in mildly hypoxic conditions, equivalent to 5,000-8,000 ft.[15] Observations made from the data (Table 3) reveal that relatively little change occurs in blood viscosity between 0-5,000 ft. However, the blood viscosity increases between 15-50% when crew members have been exposed to microgravity at altitudes of 8,000 ft. The authors concluded that the combination of hemoconcentration from PV loss and increased RBV result in increased blood viscosity. The clinical concern is that increased blood viscosity, in the setting of reduced circulation in the lower extremities and overall reduced venous system tone, may increase the risk of cardiovascular events, such as thrombi formation.[15,27,29]

**Table 3. Estimated changes in blood volume components and hematocrit based on the case of long duration exposure (chronic conditions) to both microgravity and mildly hypoxic atmospheric conditions. (Courtesy of DW Griffin, JG Meyers. Biomedical Effects of Proposed CEV Atmospheres. NASA Glenn Research Center, 2005)**

| Atm Equivalent Altitude (ft) | Change in PV (ml) | Total PV (ml) | Change in RBV (ml) | Total RBV (ml) | TBV (ml) | Hematocrit (%) | *Relative Viscosity |
|---|---|---|---|---|---|---|---|
| 0-5000 | 0 | 2764 | 0 | 1824 | 4588 | 40 | 4 |
| 6000 | -91 | 2673 | 170 | 1994 | 4667 | 43 | 4.6 |
| 7000 | -183 | 2581 | 340 | 2164 | 4745 | 46 | 5.3 |
| 8000 | -274 | 2490 | 509 | 2333 | 4823 | 48 | 6 |

*Relative Viscosity is defined as the blood's viscosity relative to that of water at 37$^{o}$C.Note that an average body mass of 68.2 kg was assumed to conform to Skylab 4 astronaut conditions on return (R+0).

However, there have been no observed or reported episodes of thrombus or embolus in either animals or humans during short or long duration spaceflight, so this concern may be only theoretical. This observation is consistent with periodic health assessment information from ISS: after the initial period of hemoconcentration that occurs during early microgravity exposure (adapting to fluid shifts and subsequent diuresis), the hematocrit normalizes (ISS crew at $ppO_2$ of 145-170 mmHg) and stays in the low normal range throughout the remainder of the mission. One means to reduce the perceived risk associated with this uncertainty is to operate the vehicle atmosphere within our existing microgravity experience base during the microgravity transit phase, then transition toward the lower habitat pressures and $ppO_2$ levels gradually. Gravity in lunar and Mars missions and its effects on pulmonary and cardiovascular physiology is another consideration, although it is not likely to have physiological significance.

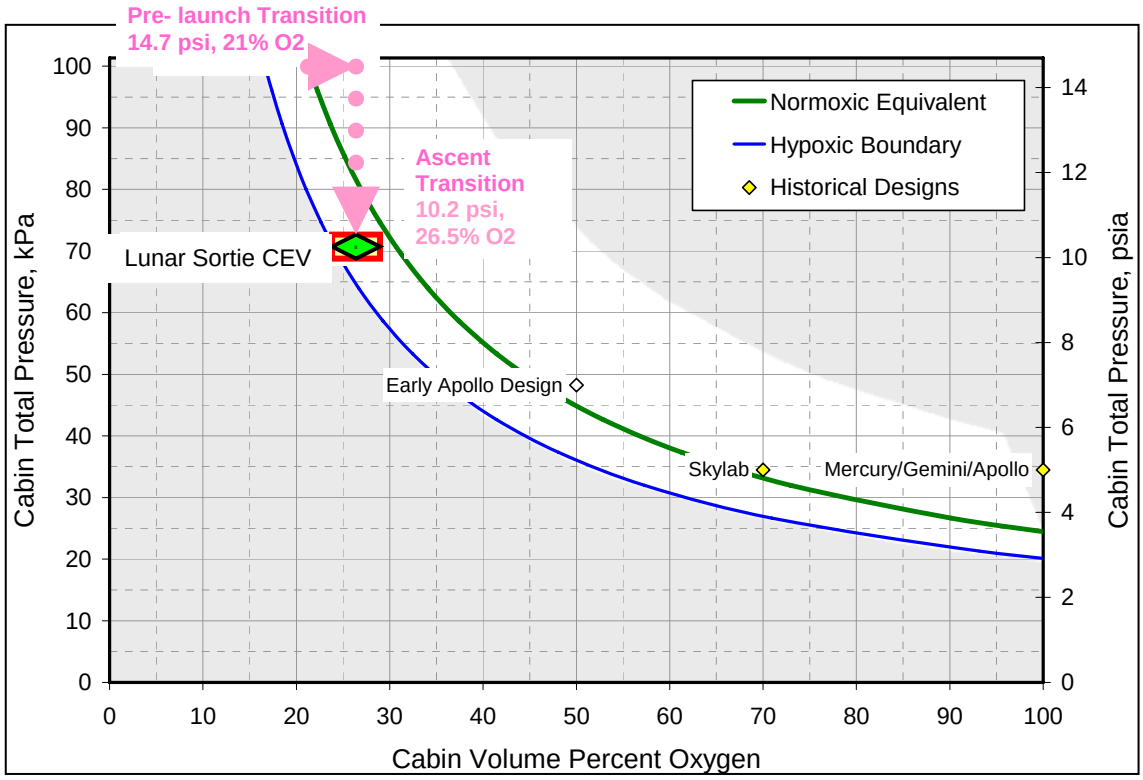
Individual susceptibility to μG adaptation in a HH environment will likely play a role in mission success (including an absence of medical problems) in these short-term missions with high EVA-rate scenarios. Some peak performance degradation could be expected in crewmembers, if $ppO_2$ is reduced acutely to less than 145 mmHg (2.8 psia), until compensation occurs. The magnitude of the performance affect will depend on the $ppO_2$, the metabolic demands of the task, and individual genetic factors. Current threshold for mandatory

supplemental $O_2$ during spaceflight operations is 111 mmHg (approx. 2.2 psia)[Ref Vol B ISS FR's.] For lunar outpost missions (approximately 6 months surface stays), full acclimatization to reduced $ppO_2$ can be expected after 30-45 days, allowing crews to function at high performance levels in the face of reduced $O_2$ tension. In summary, the lunar missions will serve to build our experience base prior to conducting the longer duration Mars missions.

### 3.3 Launch to En Route Cabin Pressure and Oxygen Concentration Changes

The proposed atmospheric transition after launch is displayed graphically in figure 1. The transition from sea level atmospheric pressure and oxygen concentration (14.7 psia and 21% $O_2$) to an en route cabin pressure and oxygen concentration range of 10.2 psia and 26.5% $O_2$ (3,500 ft) to 8.0 psia and 32% $O_2$ (5,000 ft) would likely use procedures similar to those currently practiced on shuttle and ISS missions. The launch cabin pressure would be staged down initially to ~10.2 psia and the $O_2$ enriched to ~26.5% consistent with existing shuttle and station flight rules.[23] If it was desired to reduce the $ppO_2$ to lower levels to provide for a slow acclimatization to the Lander and Habitat $ppO_2$ (~ 2.56 psi), then it should be relatively straight forward to breath down the oxygen gradually over time consistent with some TBD acclimatization protocol. During the lander/CEV docked operations the cabin pressure and $F_iO_2$ would be consistent with the CEV limitations on $O_2$ concentration (< 30%). Once the crew had transferred into the Lander and undocked from the CEV, the cabin pressure could be further reduced and the $O_2$ concentration would be elevated to 32%. There is no physiological time constraints to when this depress could occur. Consequently, there is little risk of DCS associated with this pressure transition as it is below the threshold for tissue supersaturation.

**Figure 1. Concept for Lunar-Mars CEV Atmosphere Transition on Earth Ascent. (Adapted from Henninger D, Campbell PD. Briefing to SLSD on EAWG Recommendations, January, 2006.NASA/JSC Bioastronautics Exploration Research and Technology Office)**




### 3.4 Risk of Decompression Sickness

Decompression sickness is a potentially debilitating and life-threatening condition that occurs when inert gas, typically $N_2$, evolves out of the blood and body tissues. The evolved gas can compress nocioceptive tissues causing pain ("the bends"), or interrupt venous or arterial blood flow, or other vascular and neurological disorders.[3,11] An individual is at risk of developing DCS whenever exposed to an ambient pressure lower than the tissue nitrogen tension. In order to estimate the severity of DCS, the tissue ratio,

or R-value, *R*, was developed. The R-value is defined as the ratio of the tissue nitrogen tension in 360 minute half-time tissue before depressurization to the ambient pressure after depressurization:

$$R = \frac{P_{N2\text{-}Tissue}}{P_{Suit}}$$

In general, the higher the *R*-value above 1.0, the greater the likelihood of DCS.[4,21] However, a number of other variables influence the likelihood of developing DCS, including the time the individual is exposed to reduced pressure, the degree of physical activity, the ambulation contact forces at reduced pressure, the pressure profile, repeated exposure to hypobaric pressures etc.[9] To reduce the risk of DCS when transitioning from the cabin atmosphere to the EVA suit environment, crewmembers are exposed to 100% $O_2$ for varying periods of time in an attempt to "washout" $N_2$ from the body tissue. These procedures reduce but do not entirely eliminate $N_2$ from the tissues, but do reduce the EVA crewmembers' *R*-value at the time of decompression to the lower EVA suit pressure. The current shuttle and ISS EVA suit operates at a suit pressure of 4.3 psia for maximum mobility and reduction of crewmember fatigue. It is assumed that planetary EVA suits will operate at pressures near 4.3 psia.

For the proposed habitat cabin atmospheric pressure of 8.0 psia (414.5 mmHg) at 32% $ppO_2$, the $ppN_2$ is 5.43 psia (281.9 mmHg). The *R*-value without additional in-suit prebreathe at a suit pressure of 4.3 psia is:

$$R = \frac{5.43}{4.3} = 1.23$$

The *R*-value, after a proposed maximum acceptable 60 minute in-suit 100% oxygen prebreathe, is calculated as:

$$R = \frac{4.86}{4.3} = 1.13$$

### 3.4.1 Reducing In-suit Prebreathe Time by Living in a Hypobaric and Mild Hypoxic Environment

At this time an acceptable R-value for exploration EVA's has not been determined. That determination will be made as part of an integrated approach that would first define the acceptable decompression risk for different phases of the mission (The Exploration DCS Risk Definition and Contingency Plan). The prebreathe verification tests would be conducted using an EVA simulation that is appropriate with respect to metabolic rates, time, and ambulation contact forces. In general, for a given suit pressure, the amount of prebreathe time required for a given R-value will be reduced by reducing the nitrogen partial pressure in the habitat or lander. Prebreathe time could be completely eliminated if the habitat atmosphere was 100% $O_2$. However, a balance must be achieved between the increased risk of fire at high $O_2$ concentration and the decreased risk of DCS as $N_2$ pressure in the habitat is reduced. The concentration of $O_2$ and therefore risk of fire for a given total pressure can be slightly reduced if mild hypoxia is accepted. The degree of hypoxia anticipated is equivalent to living in Denver Colorado, or Albuquerque New Mexico, at about 5,280-6000 feet altitude.

Even small reductions in the nitrogen partial pressure of the habitat can result in significant reduction in prebreathe time. To illustrate this point we compare the

prebreathe times required to achieve different R-values from different CEV and habitat atmosphere options:

I. 10.2 psia @ 26.5% $O_2$ with a 60 minute in-suit prebreathe to achieve an R-value of 1.55 for contingency EVAs from the Crew Exploration Vehicle (CEV). This is a hypobaric and mildly reduced-oxygen environment, equivalent to breathing air at 3,500 feet altitude. To achieve the same R-value as the lower habitat pressures in option II and III would require 224 and 252 minutes, respectively.

II. 8.0 psia @ 32.0% $O_2$ with a 60 minute in-suit prebreathe to achieve an R-value of 1.13 for lunar EVAs. This is a hypobaric and mildly reduced-oxygen environment, equivalent to breathing air at 5,000 feet altitude.

III. 7.6 psia @ 32.0% $O_2$ with a 60 minute in-suit prebreathe to achieve an R-value of 1.07 for Mars EVAs. This is a hypobaric and mildly reduced-oxygen environment, equivalent to breathing air at 6,500 feet altitude.

Whereas the specific acceptable R-value for exploration EVAs has yet to be determined, it is clear that reduction in habitat nitrogen partial pressure will result in a significant reduction in prebreathe time.

## 4.0 Conclusion

**The medical concerns of the integrated exploration operational atmosphere were taken into consideration in developing the EAWG recommendations, and exploration medical concurred that the current recommendations provide an**

**appropriate blend of operational enhancement and DCS risk mitigation features, that justify the slight transient risks associated with mild hypoxia and acute mountain sickness.**

Humans adapt to hypoxic exposure over a period of days to weeks (45-60 days) by increasing minute ventilation, splenic contraction, redistribution and increase in circulating blood volume, augmenting the oxygen carrying capacity of the blood.[26,27,34] The proposed mission transitions the vehicle atmospheric profile from a launch atmosphere of 14.7 psia and 21% $O_2$ to a CEV atmosphere of 10.2 @ 26.5% $O_2$ over a period of several days. The en route pressure will likely be reduced during lunar orbit in preparation for attainment of a surface cabin pressure of 8.0psia @ 32% $O_2$. Planned lunar outpost habitat pressures may be as low as 7.6 mmHg, possibly with O2 concentrations as high as 34%. The corresponding launch $P_AO_2$ (103 mmHg or 1.98 psia) to CEV (86 mmHg or 1.65 psia) and surface $P_AO_2$ (81 mmHg or 1.56 psia) represents an altitude equivalent of 3,500 ft to 5,000 ft., well within the acceptable physiological range.

However, any factor that could reduce crew health and performance should be minimized. There is not an abundance of data specific to that required for the spaceflight AMS risk assessment. There are only four reports about a $P_B$ effect *per se* on the risk of AMS induced by HH and six reports on the combined effects of HH and simulated μG adaptation that have some application here. So all conclusions listed in this summary are based on extrapolation or interpolation from limited information.

1. Although initial signs and symptoms of AMS in <u>susceptible</u> subjects are expected after acutely but sustained exposure to between 1,981 m (6,500 ft at $P_AO_2$ = 75 mmHg) and 2,590 m

(8,500 ft at $P_AO_2$ = 67 mmHg), it is likely that these would be self-limiting once acclimatization occurs.

2. At 8.0 psia (4,876 m or 16,000 ft) with a nominal $P_AO_2$ = 77 mmHg it is likely that susceptible astronauts simultaneously undergoing adaptation to μG will experience signs and symptoms of AMS.

3. No clinically significant increase in HCT or blood viscosity is expected as RBC mass, plasma, and total body water volumes adjust to the combined HH and μG environment. A transient increase to a mean HCT of about 50%, possibly as high as 55% in a particular crewperson, would be predicted based on the data for the combined effects of HH and adaptation to μG as envisioned for the CEV program. However, typical μG adapted spaceflight HCT values are in the low normal range, from 36-40% depending on gender.

4. The repeatedly validated operational experience with the Shuttle staged denitrogenation protocol at 10.2 psia (10,000 ft) while breathing 26.5% $O_2$ ($P_AO_2$ = 85 mmHg) in μG-adapted astronauts suggests that a similar low risk of AMS can be expected for the proposed CEV environment.

5. On balance, there is no definitive evidence for an exaggerated (negatively synergistic) response to the combination of HH and adaptation to μG. On the contrary, the limited evidence suggests that one stressor tends to counteract the other.

**4.1 Risk Mitigation Plan:**

There is no single study that addresses the exact conditions for the proposed nominal Constellation vehicle environment: adaptation to μG with a breathing environment at 8.0 psia (16,000 ft altitude) with 32% $O_2$ - 68% $N_2$, an acute $P_AO_2$ of about 77 mmHg. Therefore, recommendations that follow are based on extrapolations and judgment from an exhaustive literature review, but from tests that are different from the proposed CEV, LSAM, and long-duration surface habitat environments.

1. Due to the assumed lack of significant negative synergistic interaction between HH exposure with μG adaptation, expected for the proposed CEV environment. The risk of AMS is anticipated to be low, and only in a small percentage of susceptible crewmembers. If AMS was to develop, any AMS signs and symptoms would be mild, and transient, therefore no special qualification standard is required.

2. Develop the rationale and procedures to easily increase ambient $P_{B,}$ if required,

3. Use medications such as acetazolamide, dexamethasone, and supplemental $O_2$ on a countermeasure (prophylactic) to reduce AMS risk or or as-needed to provide effective treatment if required. Caution is warranted here for several reasons: acetazolamide may be prescribed for diagnosed AMS when in fact signs and symptoms are from motion sickness. Acetazolamide can have side effects due to the additional diuretic effects or altered taste sensation. Also, the inverse- medication for motion sickness may be incorrectly prescribed for AMS. AMS and motion sickness share many of the same signs

and symptoms, and may appear along similar time course. Often sleep medication is prescribed due to the many distractions in a small space vehicle. However, sleep medications are contraindicated if AMS is suspected. A sleep medication would likely worsen signs and symptoms of AMS.

3. Consider pre-flight testing to identify astronauts that are not resistant to (i.e. tolerant of) the atmospheric changes in the CEV environment, and provide special training and risk mitigation plans for those identified as susceptible, versus reassignment to a different mission.

4. Pre-adapt crews to a hypoxic environment prior to launch to blunt any combined negative effects of HH exposure with μG adaptation shortly after launch.

5. Develop an acclimatization plan through the gradual reduction in $P_AO_2$ during the initial phase of the missions, which should significantly reduce the likelihood of AMS signs and symptoms.

6. Consider inclusion of a plan to breathe 100% $O_2$ by mask over several intervals of time during the acclimatization to the μG plus HH exposure. Breathing 100% $O_2$ is shown to blunt the negative physiological effects of subsequent HH exposure.

### 4.2 Recommendations

We have provided an evidence-based approach for selecting the optimal total pressure-oxygen concentration levels for future spacecraft and habitats. Careful consideration of the current evidence reveal crewmembers will have minimal detrimental physiological effects of mildly reduced oxygen partial pressure equivalent to 3,500 ft to 5,000 feet above Earth sea level. Mission efficiency can be significantly improved under these atmospheric parameters by reducing or eliminating the dedicated oxygen prebreathe by the EVA crew. Depending on the hypobaric and mild hypoxic conditions, there is a two to eight-fold reduction in the in-suit prebreathe time to achieve the stated R-values.

These recommendations are consistent with existing NASA Shuttle and ISS standards and flight rules for breathable atmosphere and oxygen concentration, so that the CEV and habitat can be designed with no new materials limitations. The short term CEV to ISS and lunar transit missions will stay within the known operational experience base and should not require any new Earth-based physiological testing for the combined effects of microgravity and hypoxia. However, the proposed lander and habitat recommendations will require that the current NASA Standard 3000 (HSIS) total pressure and oxygen concentration limits be amended to accommodate the new environmental atmosphere ranges. These recommendations will also require materials ignition and flammability testing and certification to 34% oxygen concentration. Data collected during lunar missions (with increasing duration) will be used to formulate the plan for Mars exploration, with the assumption that the physiological interactions of reduced gravity and lower oxygen tension will be diminished as the gravity level increases on the Martian surface relative to the Moon. Implementing these recommendations, in addition to

bringing some new challenges, will provide significant improvements in operational productivity for planetary surface exploration.

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